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Original Contribution

EFFECT OF 4-HYDROXYPYRAZOLO (3,4-d) PYRIMIDINE (ALLOPURINOL) ON POSTIRRADIATION CEREBRAL BLOOD FLOW: IMPLICATIONS OF FREE RADICAL INVOLVEMENT

LORRIS G. COCKERHAM, CARMEN M. ARROYO, and JOHN D. HAMPTON
Physiology and Radiation Science Departments
Armed Forces Radiobiology Research Institute
Bethesda, Maryland 20814-5145

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Abstract—In an attempt to elucidate mechanisms underlying the irradiation-induced decrease in regional cerebral blood flow (rCBF) in primates, hippocampal and hypothalamic blood flows of rhesus monkeys were measured by hydrogen clearance, before and after exposure to 100 Gy, whole body, gamma irradiation. Systemic blood pressures were monitored simultaneously. Compared to control animals, the irradiated monkeys exhibited an abrupt decline in systemic blood pressure to 35% of the preirradiation level within 10 min postirradiation, falling to 12% by 60 min. A decrease in hippocampal blood flow to 32% of the preirradiation level was noted at 10 min postirradiation, followed by a slight recovery to 43% at 30 min and a decline to 23% by 60 min. The hypothalamic blood flow of the same animals showed a steady decrease to 43% of the preirradiation levels by 60 min postirradiation. The postradiation systemic blood pressure of the allopurinol treated monkeys was not statistically different from the untreated, irradiated monkeys and was statistically different from the control monkeys. However, the treated, irradiated monkeys displayed rCBF values that were not significantly different from the nonirradiated controls. These findings suggest the involvement of free radicals in the postirradiation decrease in regional cerebral blood flow but not necessarily in the postirradiation hypotension seen in the primate.

Keywords—Allopurinol, Cerebral blood flow, Free radicals, Hippocampus, Hypothalamus, Radiation

INTRODUCTION

Early transient incapacitation (ETI) is the complete cessation of motor performance, occurring transiently and within the first 30 min following exposure to supralethal doses of ionizing irradiation.[1] Studies have reported severe decreases in regional cerebral blood flow (rCBF) in primates at the same postirradiation time after receiving supralethal doses of gamma irradiation.[2,3] One study[4] demonstrated a dramatic fall of total cerebral blood flow following a single, 25 Gy, ^{60}Co exposure.

The irradiation-induced reduction in cerebral blood flow may employ intermediate mediators such as free radicals produced with exposure to ionizing irradiation.[5–8] Free radical interactions have been implicated in a large number of pathological conditions including irradiation injury, ischemia, microvascular injury, and cell membrane damage.[6,7,9–12] The triphasic cerebral ischemic response seen after irradiation[2,3] may be even more damaging than complete ischemia[13] since reperfusion may lead to the formation of additional free radicals.[10,12] A possible mode of pharmacologic intervention may be the introduction of superoxide dismutase[16,17] or allopurinol[15,17] since both have been used to attenuate the biochemical and functional damage usually associated with free radical production.

This study was designed to determine whether the inhibition of free radical formation via the preirradiation administration of allopurinol would be successful in altering the postirradiation hypotension and reduced rCBF. Two regions of the brain previously studied,[3,18] the hippocampus and the hypothalamus, were selected for the determination of blood flow in this study since a dramatic, postirradiation decrease in blood flow has been reported in these areas.

Correspondence should be addressed to: Lorris G. Cockerham, Ph D., Air Force Office of Scientific Research, AFOSR/NL, Bldg. 410, Bolling AFB, DC 20332-6448.

MATERIALS AND METHODS

Seventeen rhesus monkeys (*Macaca mulatta*), weighing between 2.6 and 3.8 kg (3.1 ± 0.26 SEM) were used in this study. The animals were divided randomly into three groups as follows: Group I—six sham-irradiated monkeys; Group II—six irradiated monkeys; and Group III—five monkeys given allopurinol orally (50 mg/kg) for 2 days prior to irradiation.[17] Food was withheld from all animals for 18 h before the experiment, but water was available *ad libitum*. Research was conducted according to the principles enunciated in the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources, National Research Council. The monkeys were initially anesthetized in their cages with an i.m. injection of Ketamine hydrochloride (20 mg/kg) with 0.015 mg/kg Atropine sulfate and were then moved to the laboratory where the remainder of the experiment was conducted.

A systemic venous catheter was used to administer physiological saline and the primary anesthetic, α-Chloralose (100 mg), with supplemental infusions provided as needed, based on heart rate, blood pressure, respiration rate, blood pH, and peripheral reflexes. A femoral arterial catheter was used to withdraw blood for blood chemistry and blood gas determinations and to measure systemic arterial blood pressure via a Stathem P23 Db pressure transducer.

Approximately 2 h before irradiation or sham-irradiation, the animals were intubated with a cuffed endotracheal tube and ventilated using a forced volume respirator to maintain a stable blood pH and oxygen tension. After insertion of the endotracheal tube, each animal was placed on a circulating water blanket to maintain body temperature between 36° and 38°C. A rectal probe was inserted to monitor body temperature.

The animal's head was positioned on the headholder of a stereotaxic instrument (David Kopf Instruments, Tujunga, CA) and the scalp shaved and incised, allowing access to the skull. Using the stereotaxic micromanipulator, the skull was marked for insertion of four electrodes and small burr holes were drilled through the skull at these marks. Again, using the micromanipulator, one electrode was placed in the left and one in the right hippocampus.[19] In the same manner, one electrode was placed in the left and one in the right supraoptic nucleus of the hypothalamus. The electrodes were Teflon-coated, platinum-iridium wire of 0.178 mm diameter, encased in, but insulated from, rigid stainless steel tubing (22 gauge spinal needle) with exposed tips of approximately 2 mm. The exposed dura was covered with moistened pledgetts and the electrodes were sealed and secured to the skull with dental acrylic. A stainless steel reference electrode was placed in neck tissue.

Regional cerebral blood flow was measured by the hydrogen clearance technique for 30 min before irradiation or sham-irradiation and for 60 min after.[20,21] This technique is essentially an amperometric method, which measures the current induced in a platinum electrode by the reduction of hydrogen. The current produced has a linear relationship with the concentration of hydrogen in the tissue.[22] Hydrogen was introduced into the blood via inhalation through the endotracheal tube at a rate of approximately 5% of the normal respiratory intake for each flow measurement. Blood flow was measured by each of the four electrodes every 10 min. The electrodes were maintained electrically at +600 mV in respect to the reference electrode, to reduce possible oxygen and ascorbate interference. This method has been successfully employed in several similar studies.[2,3,18]

After 30 min of recording, the animals were disconnected from the respirator and recording apparatus to facilitate irradiation in a separate room. The animals were reconnected to the respirator and recording apparatus at 4 min postirradiation or sham-irradiation and measurements were continued for a minimum of 60 min. At 30 and 10 min preirradiation or sham-irradiation, and at 6, 15, 30, 45, and 60 min postirradiation or sham-irradiation, blood samples were taken via the arterial catheter to monitor stability of blood pH and oxygen tension, and respiration was adjusted to maintain preirradiation levels. Mean systemic arterial blood pressure was determined via the arterial catheter for the duration of the experiment. After termination of the measurements, while still under anesthesia, the animals were humanely euthanized with an i.v. injection of saturated $MgSO_4$, and the electrodes examined visually via dissection for verification of placement.

Irradiation was accomplished with a bilateral, whole-body, exposure to gamma ray photons from a cobalt-60 source located at the Armed Forces Radiobiology Research Institute. Exposure was limited to a mean of 1.38 min at 74 Gy/min steady state, free-in-air. Dose rate measurements at depth were made with an ionization chamber placed in a tissue equivalent model. The measured midline tissue dose rate was 69 Gy/min, producing a calculated total dose of 100 Gy, taking into account the rise and fall of the radiation source.

Blood pressure and blood flow data were grouped into 10 min intervals, measured in relation to midtime of radiation, and plotted at the middle of the interval. The Wilcoxon Rank Sum Test was used for the statistical analysis of the data. A 95% level of confidence was employed to determine significance. Since all the animals were treated identically before irradiation or sham-irradiation, and since the preradiation data for

the control and test animals showed no significant difference. the preradiation data for the irradiated and sham-irradiated animals were combined.

RESULTS

As seen in Figure 1, the mean systemic arterial blood pressure (MABP) of untreated, irradiated animals decreased to 35% of the preradiation mean of 106.0 ± 2.3 mm Hg within 10 min postradiation. This was followed by a steady decline to a 60-min postirradiation level that was 20% of the preirradiation values. After sham-irradiation there was no significant change in MABP for the six control monkeys but the values for the group differed significantly ($p \leq 0.05$) from the other two groups. The MABP for the allopurinol treated, irradiated group did not display a statistically significant difference from the untreated, irradiated group. The respiration of each subject was maintained at preradiation levels and, although not presented, the blood gas data revealed a general stability of blood pH and oxygen tension throughout the experimental period.

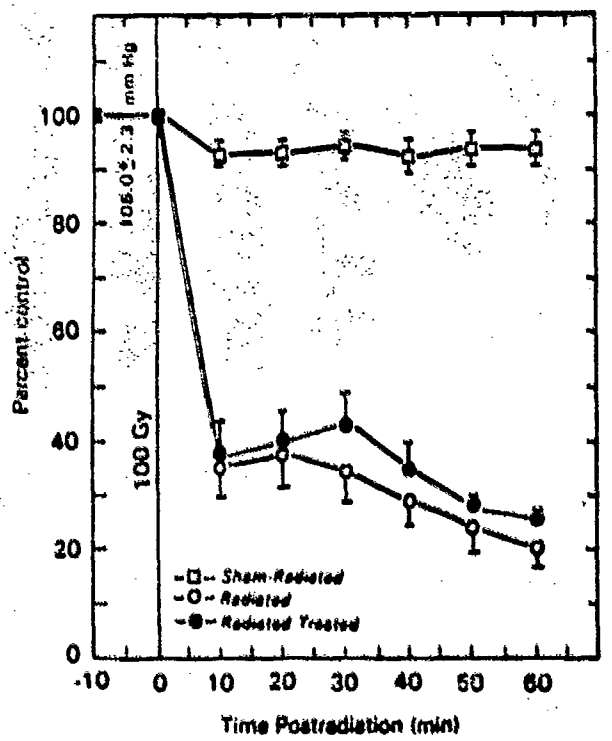

Fig. 1. Percent change in mean arterial blood pressure after exposure to 100 Gy, whole-body, gamma irradiation (±SEM), compared to a preirradiation mean of 106.0 ± 2.3 mm Hg. Animals in the sham-irradiated group ($n = 6$) were given physiological saline for 60 min before and after sham-irradiation. The untreated, irradiated group ($n = 6$) also received saline but were exposed to 100 Gy gamma irradiation. The treated, irradiated group ($n = 5$) also received saline and irradiation but were given allopurinol (50 mg/kg, orally) for 2 days prior to irradiation.

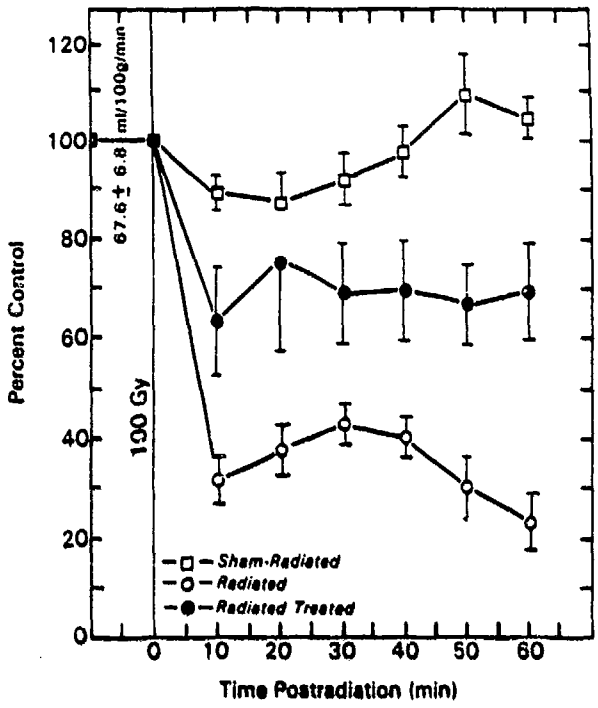

Fig. 2. Percent change in hippocampal blood flow after exposure to 100 Gy, whole-body, gamma irradiation (±SEM), compared to a preirradiation mean of 67.6 ± 6.8 ml/g of tissue/min. Animals in the sham-irradiated group ($n = 6$) were given physiological saline for 60 min before and after sham-irradiation. The untreated, irradiated group ($n = 6$) also received saline but were exposed to 100 Gy gamma irradiation. The treated, irradiated group ($n = 5$) also received saline and irradiation but were given allopurinol (50 mg/kg, orally) for 2 days prior to irradiation.

The preirradiation hippocampal blood flow, as shown in Figure 2, was 67.6 ± 6.8 ml per 100 g of tissue per min. The postirradiation blood flow for the sham-irradiated group of monkeys showed no significant changes for the 60-min observation period while the values for the untreated, irradiated monkeys showed a rapid, significant decline to 32% of the preirradiation levels by 10 min postirradiation. Following a slight increase to 43% below preirradiation levels at 30 min postirradiation, the blood flow values decreased to 23% of the preirradiation levels by 60 min postirradiation. The control and untreated, irradiated groups of monkeys were significantly different ($p \leq 0.05$) from each other at all postirradiation measurement points. The allopurinol treated, irradiated monkeys displayed a postirradiation hippocampal blood flow that decreased to only 63% of the preirradiation level at 10 min. Even though they did not drop any lower, these levels were not significantly different from the untreated, irradiated group's blood flow levels until 40 min postirradiation. Likewise, the blood flow levels of the treated, irradiated monkeys were not significantly different from those of the control monkeys until 50 min postirradiation.

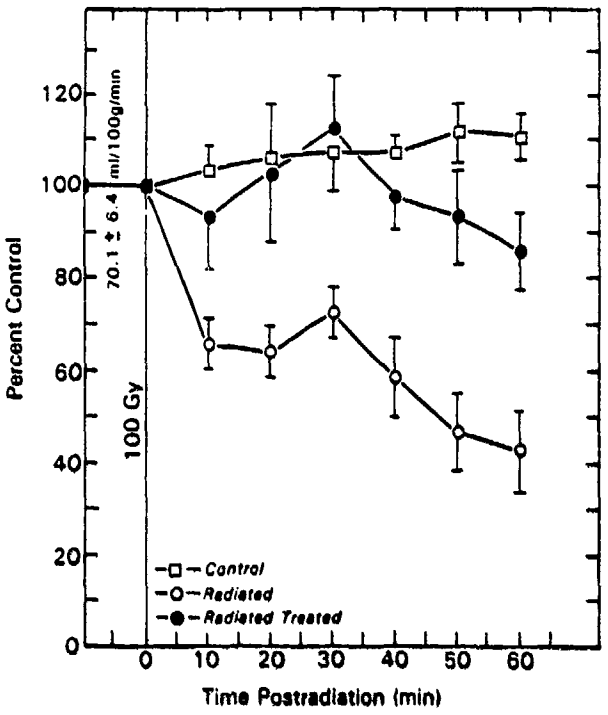

Fig. 3. Percent change in hypothalamic blood flow after exposure to 100 Gy, whole-body, gamma irradiation (±SEM), compared to a preirradiation mean of 70.1 ± 6.4 ml/g of tissue/min. Animals in the sham-irradiated group ($n = 6$) were given physiological saline for 60 min before and after sham-irradiation. The untreated, irradiated group ($n = 6$) also received saline but were exposed to 100 Gy gamma irradiation. The treated, irradiated group ($n = 5$) also received saline and irradiation but were given allopurinol (50 mg/kg, orally) for 2 days prior to irradiation.

Figure 3 displays a preirradiation mean blood flow of 70.1 ± 6.4 ml per 100 g of tissue per minute in the hypothalamus. The postirradiation blood flow for the sham-irradiated group of monkeys showed no significant changes for the 60 min observation period while the values for the untreated, irradiated monkeys showed a decline to 43% of the preirradiation levels by 60 min postirradiation. These levels became significantly different ($p \leq 0.05$) from those of the sham-irradiated group at 10 min postirradiation and remained that way for the remainder of the observations. The blood flow measurements of monkeys pretreated with allopurinol were not significantly different from those of the control monkeys at any time postirradiation. However, a significant difference was seen between the blood flow measurement of the pretreated, irradiated group and the untreated, irradiated group beginning at 40 min postirradiation.

DISCUSSION

Postirradiation hypotension has been well documented in the rhesus monkey and a critical postirradiation mean arterial blood pressure (MABP) of 50%–60% of the preirradiation MABP must be maintained for adequate autoregulation of cerebral circulation.[4,23,24] The initial precipitous decline in MABP to 35% of the preirradiation levels may then be associated with the similar immediate decrease in blood flow seen in both the hippocampus and hypothalamus of the untreated, irradiated animals. In fact the decline in MABP and cerebral blood flow (CBF) reported here corresponds closely in time with the observed occurrence of ETI[23,25,26] and suggests a causal relationship between the depressed MABP, CBF and the appearance of ETI.

Autoregulation of cerebral blood flow appeared to be intact in animals pretreated with allopurinol, even though the postirradiation MABP fell to approximately 35% of the preirradiation level. The difference noted in the effect of allopurinol in the hippocampus and the hypothalamus may be attributed to the presence of fenestrations of the blood–brain barrier near the hypothalamus.[27,28] These fenestrations, or windows, would allow the preirradiation administered allopurinol to enter the hypothalamus before irradiation. Their absence in the area of the hippocampus would inhibit the entrance of allopurinol into that area until after the irradiation-induced alteration of the blood–brain barrier.[29] Therefore, the radioprotective effect of allopurinol would be present in the hypothalamus at the time of irradiation, but not in the hippocampus until after irradiation.

Allopurinol interferes with the xanthine oxidase catalyzed production of free radicals and has been used to attenuate cellular damage associated with the reperfusion induced production of free radicals.[30,31] This action would have been expected during the partial cerebral reperfusion that occurred between 10 and 30 min postirradiation. However, the administration of allopurinol altered the immediate postirradiation decrease in cerebral blood flow, thereby eliminating the reperfusion-xanthine oxidase production of free radicals. It is therefore highly likely that the immediate action of allopurinol may have been by some means other than xanthine oxidase inhibition.

A possible explanation of the mechanistic effect of allopurinol in diminishing the postirradiation decrease in rCBF is an interference in the formation of superoxide radicals. Superoxide radicals can be generated in the reaction of hydrated electrons or hydrogen atoms with dissolved oxygen following gamma irradiation of aqueous solutions. This radiolytically-formed free radical is involved in oxidative chain reactions[32] with the possibility of interconversion and postirradiation generation of other forms of activated oxygen, leading indirectly to further irradiation-induced cellular damage.[33] A possible mode of pharmacologic intervention may well be the introduction of allopurinol to intervene

in the production of free radicals, thereby explaining why treatment with allopurinol would maintain rCBF during the entire observation period even with the presence of profound hypotension in treated animals at 60 min. Thus, the allopurinol prevention of irradiation-induced free radical formation would allow the maintainance of rCBF in the initial 20–30 min. Thus, the allopurinol prevention of irradiation-induced free radical formation would allow the maintainance of rCBF in the initial 20–30 min. Therefore, there would be no reperfusion-induced formation of additional free radicals, allowing the rCBF to be maintained during the second portion of the observation period.

Examination of the chemical/physical structure of allopurinol suggests that its effectiveness may be due to an ability to scavage hydrated electrons and hydrogen atoms that would react with oxygen to form superoxide. Certainly, this may be elucidated further with spin trapping experiments in gamma irradiated aqueous solutions of allopurinol in the presence of a spin trap such as DMPO (5,5-dimethyl-1-pyroline-1-oxide). This spin trapping [34] consists of reacting a short-lived free radical, such as superoxide, with a spin trap, usually a nitrone or nitroso compound, producing a longer-lived nitrooxide radical which can be detected and identified by electron spin resonance (ESR).

In conclusion, we have shown that the administration of allopurinol will alter significantly the postirradiation-reduced regional cerebral blood flow without affecting the irradiation induced hypotension. We have also introduced a theoretical mechanism through which the administration of allopurinol may prevent an irradiation-induced reduction in rCBF. The next logical step will be to show that allopurinol actually does prevent the irradiation-induced production of free radicals. Further study with spin trapping experiments may be able to elucidate the mechanism.

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